BASIC SCIENCE REVIEW

THE STRUCTURE AND FUNCTION OF THE CARDIAC MYOCYTE: A REVIEW OF FUNDAMENTAL CONCEPTS

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The myocardium is highly organized tissue, composed of several cell types that include smooth muscle cells, fibroblasts, and cardiac myocytes. The fundamental contractile cell of the myocardium is the myocyte. The purpose of this review is to examine the structural components of the myocyte and then to place these components into a functional context with respect to the contractile process.

Basement membrane

The first boundary encountered when moving from the extracellular space to the intracellular space of the myocyte is the basement membrane. The basement membrane is composed primarily of type IV collagen, the glycoproteins laminin and fibronectin, and proteoglycans.[1] The basement membrane provides an interface to the fibrillar collagen matrix of the extracellular space with anchoring fibers, which bind the basal lamina to underlying collagen. The function of the basement membrane is to provide an initial barrier that will influence the exchange of macromolecules between the extracellular space and the myocyte. Another important function of the basement membrane is to provide an interface for myocyte adhesion and continuity with the extracellular matrix. An illustration of the organization of the pertinent structures of the cardiac myocyte is shown in Fig 1.

Sarcolemma

A specialized structure of the myocyte is the sarcolemma, a coalescence of the plasma membrane proper and the basement membrane. The sarcolemma is composed of a lipid bilayer, which contains hydrophilic heads and hydrophobic tails. This configuration allows the sarcolemma to interact with the intracellular and extracellular environment, but a hydrophobic core results in the sarcolemma being impermeable to charged molecules. Interwoven throughout the sarcolemma are integrins, which, with receptor transmembrane proteins, bind the myocyte to the extracellular matrix and basement membrane. More important, integrins attach to the intracellular side of the sarcolemma, forming an important collagen-integrin-cytoskeletal relation.[2] It has been postulated that integrin engagement to the extracellular and intracellular spaces is an essential component for the transduction of myocyte shortening into an overall ventricular ejection.[2]

The sarcolemma forms 2 specialized regions of the myocyte, the intercalated disks and the transverse tubular system. The intercalated disks are a specialized cell-cell junction, which serves both as a strong mechanical linkage between myocytes and as a path of low resistance that allows for rapid conduction of the action potential between myocytes.[3] Transverse tubules, or T tubules, are invaginations of the sarcolemma into the myocyte, which form a barrier between the intracellular and extracellular spaces. These extensions bring in close apposition the L-type Ca^{2+} channel and the sarcoplasmic reticulum Ca^{2+} discharge system, thus making the T-tubular system an important structural component in excitation-contraction coupling.

As with most lipid bilayers, the fundamental function of the sarcolemma is to provide a barrier for diffusion. The sarcolemma also contains membrane proteins, which include receptors, pumps, and channels. This is a specialized feature of the sarcolemma and is essential to the contractile process of the myocyte. Presented below is an overview of the sarcolemmal proteins that are essential to the propagation of the myocyte action potential and, therefore, fundamental to the contractile process.

Sarcolemmal pumps and ion channels. A useful paradigm to review the pumps and channels of the

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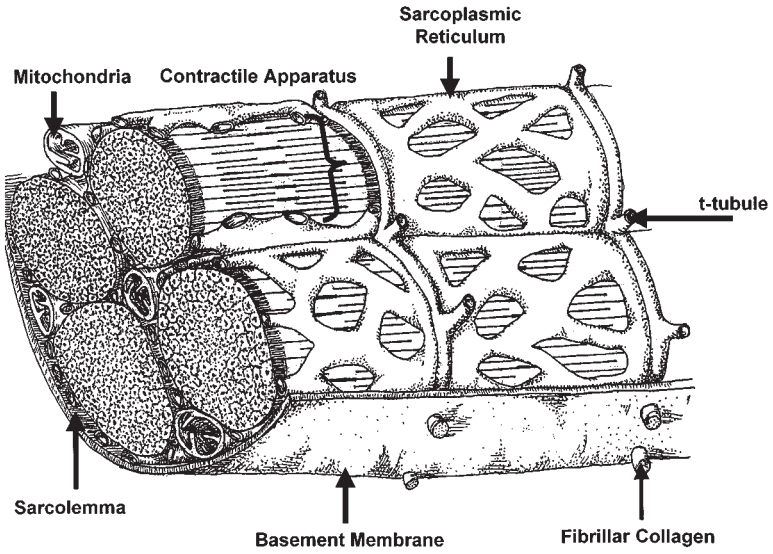

Fig 1. Longitudinal cross section of an individual cardiac myocyte. The sum of the integral parts of the cardiac myocyte are shown here, moving from outward in. The basement membrane, which is composed of collagen, glycoproteins, and proteoglycans, provides an interface for myocyte adhesion, as well as continuity with the extracellular matrix. The basement membrane serves as an anchoring site for the collagen fibrils. The sarcolemma, which enfolds the myocyte, contains integrins that bind the myocyte to the extracellular matrix, and also contains integral proteins that contribute to the action potential. Invaginations of the sarcolemma, which contains a high density of L-type Ca^{2+} channels, are the T tubules. This specialized region of the sarcolemma allows for the close apposition of the L-type Ca^{2+} channel to the Ca^{2+} release channels of the sarcoplasmic reticulum. The sarcoplasmic reticulum serves both as a source and an internal store of cytosolic Ca^{2+} required for excitation-contraction coupling. The contractile apparatus is a highly organized array of myofilament proteins composed primarily of thick myosin and thin actin filaments. The overlapping of these proteins form the dark and light bands as shown in this illustration. Cut in cross section are shown the numerous mitochondria, which are in close proximity to the myofilament apparatus.

myocyte sarcolemma is to place it in the context of the phases of the action potential. A representative ventricular myocyte action potential is shown in Fig 2. The resting membrane potential, or phase 4 of the action potential, is maintained primarily by the inward K^+ rectifier and is secondarily influenced by the Na^+/K^+ adenosinetriphosphatase (ATPase), the Na^+/Ca^{2+} exchanger, and the sarcolemmal Ca^{2+} ATPase. During this phase, the sarcolemma is permeable only to K^+; thus it is the K^+ equilibrium potential that primarily determines the resting membrane potential of the myocyte. The inward K^+ rectifier allows for K^+ diffusion into the myocyte. The Na^+/K^+ ATPase generates a net outward current through the extrusion of three Na^+ ions for two K^+ ions, as well as being the site for digitalis binding. The Na^+/Ca^{2+} exchanger and the sarcolemmal Ca^{2+} ATPase provide the basis for Ca^{2+} extrusion from the myocyte. The Na^+/Ca^{2+} exchanger is a bidirectional channel, with the relative amounts of either ion carried across the membrane determined by the concentrations on either side of the membrane.[4] However, the Na^+/Ca^{2+} exchanger is the primary system for Ca^{2+} efflux from the myocyte.[4-6] Through the removal of cytosolic Ca^{2+}, the balance of Ca^{2+} efflux and influx can be maintained, contributing to the maintenance of the resting potential.

The fast Na^+ channel is responsible for the rapid upstroke of phase 0 of the action potential. When the membrane potential achieves a preset threshold voltage, the Na^+ channels rapidly activate (<1 ms) and remain activated for a duration of only 2 to 10 ms; thus the name "fast" Na^+ channel. The activation of these channels allow Na^+ to flow into the cell along both electrical and chemical concentration gradients. This influx of Na^+ through the fast Na^+ channel puts into motion the ionic processes responsible for the other phases of the action potential.

Rapid inactivation of the Na^+ channels and slower activation of two outward currents are the bases for early repolarization. The positive membrane potential,

the Cl^- concentration gradient, and increased membrane permeability to Cl^- allows for the entry of Cl^- into the cell. In addition, a transient efflux of K^+ through specific channels occurs along the K^+ electrochemical gradient. The combination of these three events contributes to a brief and small repolarization of the membrane potential during phase 1 of the action potential.

The cardiac action potential plateau, or phase 2, is primarily determined by the influx of Ca^{2+} through the L-type Ca^{2+} channels.[7,8] In addition, a counterbalancing outward K^+ current flows through the "anomalous" K^+ rectifier.[3] Both of these channels are activated during the upstroke of the action potential and reach peak current concurrently during the plateau phase. L-type Ca^{2+} channels are intimately involved in excitation-contraction coupling, which will be discussed in a later section.

Phase 3 or repolarization is the result of increased K^+ conductance through the delayed rectifier K^+ channels. These channels are activated toward the end of the plateau phase and allow K^+ ions to flow along the concentration gradient. All other inward currents, Na^+ and Ca^{2+}, are inactivated, thus making the delayed rectifying K^+ current responsible for the restoration of the membrane potential to the resting state. By means of an adenovirus transfer method, increased gene expression for the K^+ channel has been induced in adult ventricular myocyte preparations.[9] Increased expression of the K^+ channel resulted in significant shortening of phase 3 of the action potential and abbreviated the excitation-contraction coupling process.

Sarcolemmal receptor systems. Receptor systems that have been identified in the myocyte include the muscarinic, α, and endothelin receptor systems.[10-12] However, one of the more important receptor systems of the myocyte is the β-adrenergic system, because modulation of this receptor transduction system is commonly used in clinical practice. For the purposes of this review, the β-adrenergic receptor system can serve as a prototypical sarcolemmal receptor transduction system. The β-adrenergic receptor system exists in both activated and inactivated states. Under ambient conditions, both forms are in equilibrium, but the inactivated state is predominant.[13,14] Endogenous catecholamines and synthetic β-adrenergic agonists bind to the β-adrenergic receptor, resulting in a 3-dimensional conformational change of the receptor. This begins with the binding and activation of a guanine nucleotide–dependent coupling protein, resulting in adenylate cyclase stimulation and subsequent increases in cyclic adenine monophosphate production. Through the binding of the regulatory subunit, cyclic adenine monophosphate stimulates the active catalytic subunits

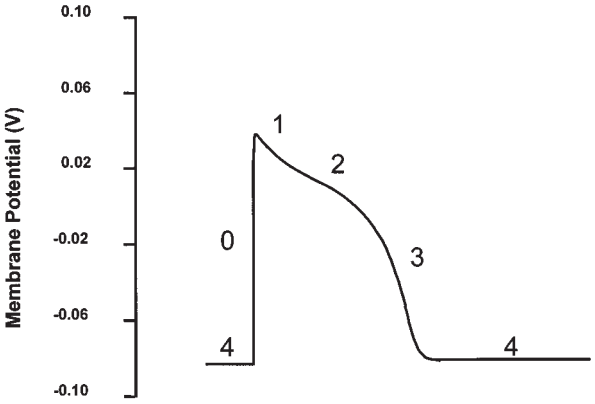

Fig 2. A schematic of a ventricular myocyte action potential. The regenerative cardiac action potential consists of 5 phases. Phase 0, the upstroke, corresponds to rapid depolarization. The upstroke is followed by phase 1, a brief early repolarization, phase 2 or plateau, phase 3 or rapid repolarization, and phase 4, which corresponds to the resting membrane potential. This action potential is the result of sarcolemmal protein interactions that have been summarized in the text.

of protein kinase A, which in turn phosphorylates specific sites within the myocyte to modify their activity.[15-17] Three phosphorylation sites relevant to the excitation-contraction coupling process are the sarcolemmal L-type Ca^{2+} channel, the sarcoplasmic reticulum regulatory protein, phospholamban, and troponin I of the myocyte contractile apparatus. In a study by Bittner and associates,[18] transgenic mice were created with specific myocardial overexpression of the human β-adrenergic receptor. These mice exhibited increased basal myocardial adenylate cyclase activity, which translated into enhanced left ventricular contractility. In addition, Rockman and coworkers[19] found that the overexpression of the β-adrenergic receptor resulted in markedly enhanced myocardial relaxation, as well as a reduction in the levels of the sarcoplasmic protein phospholamban. These genetic models emphasize the importance of the β-adrenergic receptor transduction system in the modulation of the myocyte excitation-contraction coupling process.

Myocyte cytoskeleton

The cytoskeleton of the myocyte forms an important structural interface with the extracellular environment and the contractile apparatus.[20-22] Specifically, a number of cytoskeletal proteins such as α-actinin, talin, and desmin converge at the site where integrins enter the cytosolic compartment. A number of these cytoskeletal proteins can be phosphorylated and thereby change structural conformation, which in turn can influence

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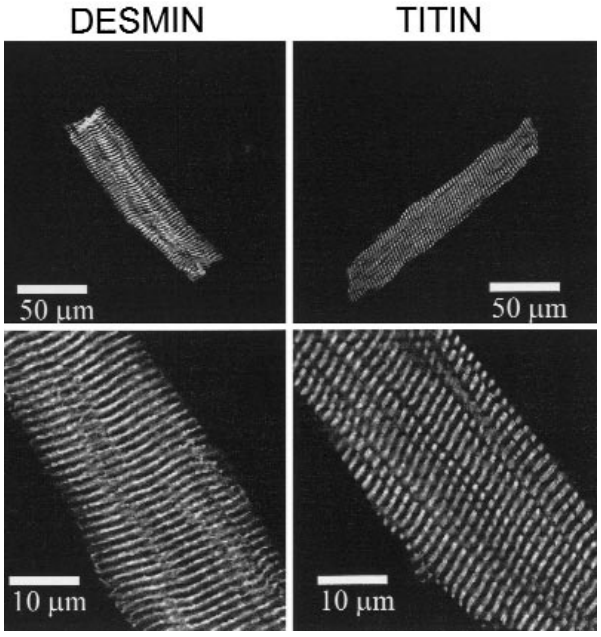

Fig 3. The cytoskeleton of the myocyte is highly structured and is composed of a number of proteins that participate in signal transduction, the maintenance of cell shape, and serve as a template for contractile element assembly. In this figure, immunofluorescent images for the cytoskeletal protein desmin *(left panels)* and titin *(right panels)* are shown. Desmin is an intermediate filament that co-localizes to the Z-bands of myocytes and has been postulated to provide alignment of adjacent myofibrils. The periodicity of desmin within the myocytes can be readily appreciated at high power *(lower left panel).* Titin is the largest cytoskeletal protein identified within the myocyte and plays an important role in maintaining sarcomere alignment, provides elastic recoil, and prevents sarcomere overstretch. A doublet pattern for titin can be appreciated at high power *(lower right panel),* which interfaces on either side of the Z-band at 100 nm intervals.

myocyte geometry and function. Moreover, large cytoskeletal proteins such as titin provide viscoelastic properties to the myocyte and have been postulated to prevent overstretch of the myofilament apparatus.[23,24] Fig 3 presents representative photomicrographs of a normal myocyte after immunofluorescent staining for the cytoskeletal proteins desmin and titin. Other important cytoskeletal proteins include the tubulins. Specifically, α- and β-tubulin participate in myofibrillar assembly and the transduction of mechanical signals to the nuclear envelope.[25] More recently, it has been demonstrated that the density and organization of β-tubulin within the myocyte may directly influence myocyte contractile performance.[26] Thus, although the cytoskeleton has been historically considered to be a static component of the myocyte, it is very likely that the complex interaction of cytoskeletal proteins directly affect the form and function of the myocyte.

Sarcoplasmic reticulum

The sarcoplasmic reticulum, an intracellular membrane network, is a highly efficient Ca^{2+} handling organelle, specialized for the regulation of cytosolic Ca^{2+} concentration.[27,28] It forms specialized structural regions of the myocyte in close apposition with the sarcolemma, particularly, the T tubular system.[29] The sarcoplasmic reticulum, responsible for the Ca^{2+} source in excitation-contraction coupling,[15] contains three important components that participate in the role of this organelle with respect to Ca^{2+} homeostasis: the sarcoplasmic reticulum Ca^{2+} ATPase (SERCA-2), the regulatory protein of SERCA-2, phospholamban, and the Ca^{2+} release channel.

Sarcoplasmic reticulum proteins. SERCA-2, an ATP-dependent Ca^{2+} pump distinct from that found in the sarcolemma, is a fundamental determinant of Ca^{2+} accumulation within the myocyte.[3] For every 1 mol of ATP hydrolyzed, 2 mol of Ca^{2+} is transported back into the sarcoplasmic reticulum, thereby decreasing cytosolic Ca^{2+}.[30,31] In conjunction with the Na^+/Ca^{2+} exchanger and sarcolemmal Ca^{2+} ATPase, the uptake of Ca^{2+} by SERCA-2 forms the basis by which cytosolic Ca^{2+} can be altered by more than 100-fold during the excitation-contraction coupling process.[16] Phospholamban, co-localized with SERCA-2,[32] has only recently been recognized as an important regulatory protein for SERCA-2 function. When phosphorylated, phospholamban facilitates SERCA-2 uptake into the sarcoplasmic reticulum, whereas dephosphorylation of phospholamban results in decreased sensitivity of SERCA-2 to cytosolic Ca^{2+}.[28] Thus the phosphorylated state of phospholamban plays a critical role in the rate and extent of Ca^{2+} removal from the cytosolic compartment. Using a genetically engineered mouse model, in which endogenous phospholamban had been increased by more than 2-fold, important changes in the Ca^{2+} uptake process were observed.[33] Specifically, a reduction in the affinity of SERCA-2 for Ca^{2+} occurred and caused a decline in the magnitude of the Ca^{2+} signal.[33] These changes in SERCA-2 function with phospholamban overexpression were translated into diminished active relaxation of the myocyte.[33] Thus phospholamban plays a critical role in the regulation of Ca^{2+} uptake in the sarcoplasmic reticulum, which in turn regulates the fundamental process of excitation-contraction coupling. The calcium release channel is found in dense populations at the interface between the sarcoplasmic reticulum and the T-

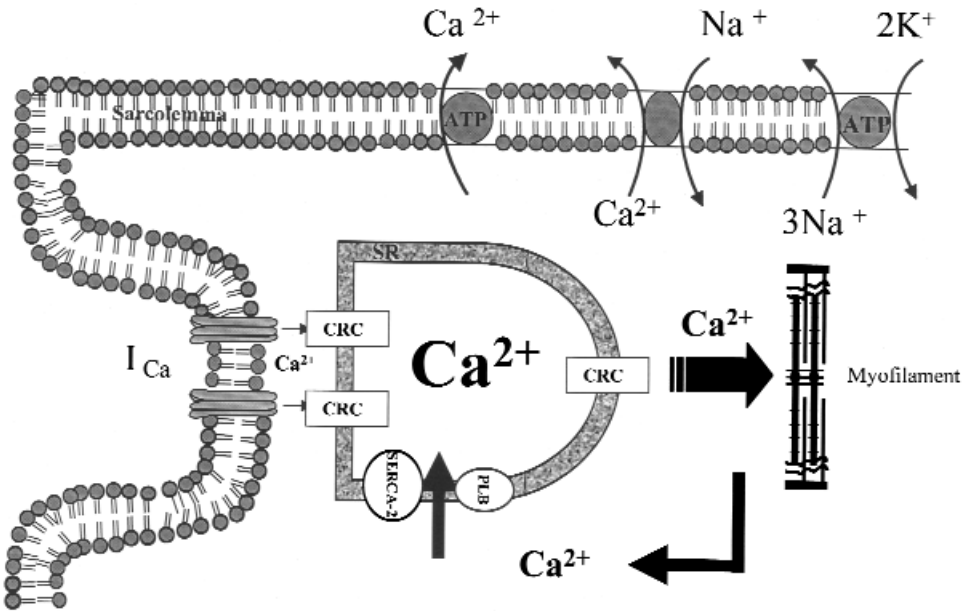

Fig 4. A schematic of the components that participate in excitation-contraction coupling in the cardiac myocyte. The sarcolemma contains a number of ion channels and pumps that contribute to overall Ca^{2+} levels within the myocyte. The mechanisms that contribute to removal of Ca^{2+} from the myocyte include the Na^+/Ca^{2+} exchanger and the sarcolemmal Ca^{2+}-ATPase. The Na^+/Ca^{2+} exchanger is influenced by either ion concentration and is reversible. The Na^+/K ATPase contributes to the extrusion of Na^+ and thereby contributes to the maintenance of the resting membrane potential. With myocyte depolarization, the voltage-sensitive Ca^{2+} channel (L-type Ca^{2+} channel) will become active and result in a Ca^{2+} current (I_{CA}). The Ca^{2+} current is a "trigger current" that will result in activation of the Ca^{2+} release channel *(CRC)* on the sarcoplasmic reticulum. The bolus of Ca^{2+} released from the Ca^{2+} release channel results in engagement of the myofilaments and actin-myosin crossbridge formation. Removal of Ca^{2+} from the cytosolic space, thereby disengaging crossbridge formations, is intimately dependent on the action of the sarcoplasmic reticulum Ca^{2+} ATPase (SERCA-2). (Modified from Bers DM. Excitation-Contraction Coupling and Cardiac Contractile Force, Fig 21, 1991: p. 38. With kind permission from Kluwer Academic Publishers.)

tubular system of the sarcolemma.[34] This channel, also called the ryanodine receptor channel,[15,34,35] is responsible for Ca^{2+} release from sarcoplasmic reticulum stores and is very sensitive to small changes in cytosolic Ca^{2+}. A small but rapid influx of Ca^{2+} through the Ltype Ca^{2+} channel will result in an immediate release of a large bolus of Ca^{2+} into the myocyte cytosolic space.[3] This large release of Ca^{2+} from the calcium release channel is responsible for engaging the contractile apparatus.[34-36]

Contractile apparatus

The fundamental contractile unit within the myocyte is the sarcomere, containing the components of the contractile apparatus. The sarcomere is composed of thick and thin interdigitating filaments and has a resting length of 1.8 to 2.4 μm.[16] The fundamental proteins of the contractile apparatus are myosin, actin, tropomyosin, and the troponin complex.[16] In the presence of increased extracellular Ca^{2+}, interactions occur between these proteins, causing the hydrolysis of ATP and changes in physical-chemical dynamics. These processes result in the development of tension within the myocyte. Myosin, the thick filament, is composed of a filamentous tail and a globular head region. This globular head contains the site for actin binding, as well as a catalyzing site for ATPase activity. Actin is the major contractile protein found in the thin filament. Having two forms, G and F, F-actin is the backbone of the thin filament with G-actin working as a stabilizing protein. Each G-actin monomer has two myosin binding sites. The interaction between the myosin globular head and the G-actin monomer in the presence of ATP results in crossbridge formation and sarcomere shortening. Tropomyosin is another protein found in the thin filament. This rigid molecule lies on either side of

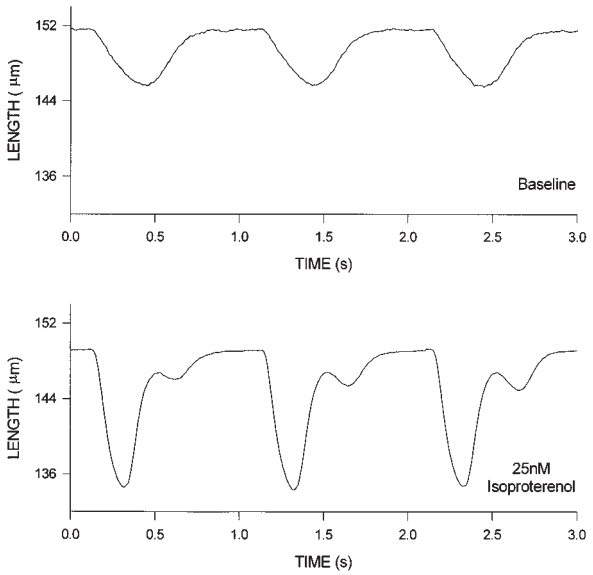

Fig 5. A representative contraction profile of an isolated normal human left ventricular myocyte stimulated at 1 Hz under normothermic contractile conditions. A uniform pattern of contractility can be appreciated. After β-adrenergic receptor stimulation (25 nm isoproterenol), the extent of myocyte shortening is significantly increased, consistent with a positive inotropic response. The increase in contractility that occurs in response to inotropic stimulation is due to phosphorylation of 3 key proteins within the myocyte: the sarcolemmal L-type Ca^{2+} channel, the sarcoplasmic reticulum regulatory protein, phospholamban, and troponin I of the myocyte contractile apparatus.

actin, adding rigidity to the thin filament. Tropomyosin influences actin-myosin crossbridge formation by physically interdigitating between the actin-myosin cleft, thus preventing Ca^{2+} binding.[3] The troponin complex, also present in the thin filament, is composed of three proteins: troponin T, I, and C. Troponin is an important component in that it regulates the extent of crossbridge formation, as well as contributing to the structural integrity of the sarcomere. Troponin T binds the troponin complex to tropomyosin and anchors the complex to the thin filament. Under normal conditions, phosphorylated troponin I weakens the affinity of Ca^{2+} for troponin C. Ca^{2+} binding to troponin C results in a conformational change of the complex, with subsequent actin-myosin interaction, thus initiating crossbridge formation.

Mitochondria

The maintenance of high ATP stores is a requirement of the myocyte. Thus the myocyte is rich in the organelle essential for this process—the mitochondria. Mitochondria occupy 40% of myocyte cell volume,[3] thus emphasizing the immense energy demands of the myocyte. Phosphocreatine is a high-energy reserve and also plays an instrumental role in the shuttling of phosphate to the cytosol.[3] Because cytosolic phosphocreatine and creatine concentrations are higher than those of adenosine diphosphate, this serves as a rapid transport system of high-energy phosphate between the mitochondria and the cytosol. The high-energy phosphate of ATP is transferred to phosphocreatine, which diffuses through the cytosol to be reconverted to ATP for cell energy use, for example, in excitation-contraction coupling.[3] Mitochondria are also known to have the capacity to bind and take up large amounts of cytosolic Ca^{2+}, as well as play a role in the buffering of cytosolic Ca^{2+}, thus protecting the myocyte from the effects of Ca^{2+} overload.[3,37]

Excitation-contraction coupling

Excitation-contraction coupling refers to the mechanism by which an action potential leads to contraction of the myocyte. The fundamental ion for inducing the excitation-contraction coupling complex is Ca^{2+}. The excitation-contraction coupling complex is achieved through the increase in cytosolic Ca^{2+} levels from nanomolar (100 nmol/L) to micromolar (10 μmol/L) concentrations.[16] Fig 4 presents important components of the excitation-contraction coupling process.

Contraction. When an action potential reaches the myocyte, the wave of depolarization, particularly at the T-tubular system, results in the activation of sarcolemmal voltage-sensitive L-type Ca^{2+} channels and Ca^{2+} conductance.[7,8] This rapid but small influx of Ca^{2+} through the L-type Ca^{2+} channels causes activation of the Ca^{2+} release channel, resulting in an immediate release of large amounts of Ca^{2+} into the cytosol.[7,15,34-36,38,39] The Ca^{2+} that flows through the L-type Ca^{2+} channel is referred to as the trigger Ca^{2+} current.[7,16] The absolute amount of trigger Ca^{2+} is very small in relation to Ca^{2+} release from the sarcoplasmic reticulum; therefore, trigger Ca^{2+} does not significantly contribute to crossbridge formation.

After release of Ca^{2+} from the sarcoplasmic reticulum, a series of interactions occur within the contractile protein of the sarcomere. For the purposes of this review, the sliding filament theory will be used to explain the interaction of the various contractile proteins.[3,16,17,40] Under resting conditions, concentrations of cytosolic Ca^{2+} are low; phosphorylated troponin I decreases the affinity of cytosolic Ca^{2+} for troponin C, favoring a stronger interaction between troponin I and

the actin molecule. Therefore the troponin-tropomyosin complex is shifted toward the outer grooves of the actin filament, thus blocking actin-myosin interaction. An increase in cytosolic Ca^{2+} allows for the binding of Ca^{2+} to troponin C, resulting in a shift of troponin I affinity from the actin filament to troponin C. The destabilizing of troponin I from the actin molecule results in a conformational shift of the troponin-tropomyosin complex away from the actin-myosin binding site with subsequent crossbridge formation. After crossbridge formation, the hinge regions in the crossbridge permit the myosin head to swing toward the thin filament. After attachment, the myosin head changes conformation, resulting in the hydrolysis of ATP. This conformational change in the crossbridge generates a force moving the thin filament relative to the thick filament. This crossbridge formation and the conformation change of the myosin head results in the hydrolysis of ATP and the binding of a new ATP molecule. The binding of new ATP causes release of the existing crossbridge and formation of a new one. Each crossbridge cycle moves the filaments approximately 10 nm with an average velocity of 0.98 μm/s. If the average sarcomere length is considered to be 1.8 μm,[3,38] the speed of sarcomere contraction translates to 5.645×10^{-6} miles per hour. Although this may seem relatively slow, when velocity is normalized to the initial sarcomere length, sarcomere velocity is actually 1960 units of distance per hour. This highly dynamic process is dependent on the number of crossbridges formed during each contraction, the action potential duration, the amount of Ca^{2+} released from the sarcoplasmic reticulum, and ATP stores. The cycle of crossbridge formation will continue until the Ca^{2+} is removed from the cytoplasm by active, energy-dependent means or by exhaustion of ATP stores.

Active relaxation. Active relaxation is dependent on the function of SERCA-2. For each 1 mol of ATP hydrolyzed, 2 mol of Ca^{2+} is transported back into the sarcoplasmic reticulum. The function of SERCA-2 and the regulatory state of phospholamban significantly influence the active relaxation process within the myocyte. Other systems, albeit slower, for the removal of Ca^{2+} from the cytosolic compartment include the Na^{+}/Ca^{2+} exchanger, the sarcolemmal Ca^{2+} ATPase, and additional cytosolic Ca^{2+} binding proteins including calmodulin and calsequestrin. The complex formed by the binding of calmodulin to intracellular Ca^{2+} can activate the sarcolemmal Ca^{2+} ATPase to extrude cytosolic Ca^{2+}.[41,42] Calsequestrin binds and internalizes Ca^{2+} within the internal cardiac vesicular stores where it is located.[27,41] It is important to emphasize that active relaxation is a high energy–dependent process, and changes in this phase of excitation-contraction coupling will be manifest as changes in myocyte diastolic performance.

Myocyte contractility

The end result of a successfully transduced action potential and the initiation of Ca^{2+} release into the cytosolic compartment of the myocyte is a contraction. Over the past decade, refinements in isolation methods,[43] culture techniques, and computer acquisition systems have made it possible to measure contractile function at the single myocyte level.[44,45] The isolated myocyte provides a measure to examine the modulating effects of the sarcolemmal receptor systems with respect to contractile performance in the absence of confounding factors, such as loading conditions and neurohormonal activity. For example, the direct effects of β-adrenergic receptor stimulation, as well as modulating downstream factors in the β-adrenergic receptor transduction pathway, have been more recently examined.[46] Specifically, a left ventricular myocardial biopsy specimen taken at the time of cardiac surgery can be used to isolate myocytes and measure contractile performance. It has been shown that viable, quiescent isolated human left ventricular myocytes can be obtained from this application and have the ability to respond to electrical stimulation in an appropriate manner (Fig 5). Moreover, these left ventricular isolated myocyte preparations can provide a means of studying the contractile effects of β-adrenergic receptor stimulation. As shown in Fig 5, β-adrenergic receptor stimulation (25 nm isoproterenol) of normal isolated left ventricular myocytes produced an inotropic response consistent with the physiologic effects of β-receptor transduction. It is likely that these isolated myocyte studies will provide important insight into the mechanisms that regulate the excitation-contraction coupling process in normal and pathologic conditions relevant to the cardiothoracic surgeon.

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